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Pacing for syncope: what role? which perspective?

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Cardiac pacing is the most effective therapy to prevent syncopal recurrences when syncope is due to bradycardia. Causes of bradycardia-induced syncope are intrinsic [primary dysfunction of the atrioventricular (AV) conduction system and of sinus node function] and extrinsic (vagal reflexes). Intrinsic and extrinsic mechanisms often coexist in the same patient, especially in the case of sick sinus syndrome. Although formal randomized controlled trials have not been performed, cardiac pacing is commonly considered very effective and therefore accepted as therapy of choice in all patients in whom an AV block is responsible for syncope. Cardiac pacing is also commonly indicated in patients in whom syncope is caused by sick sinus syndrome or carotid sinus syndrome. However, owing to the frequently associated vasodepressor reflex, syncope still recurs during long-term observation in $\sim$20% of the patients. Despite several controlled trials, the indications for cardiac pacing are still controversial in patients with vasovagal syncope (VVS). To date, cardiac pacing may be only indicated in selected older patients affected by VVS who present with severe recurrent impredictable syncopal attacks affecting quality of life. Also in these patients some rare syncopal recurrence should be expected over the long term.

Introduction

Cardiac pacing is the most effective therapy to prevent syncopal recurrences when syncope is due to bradycardia. Causes of bradycardia-induced syncope are intrinsic [primary dysfunction of the atrioventricular (AV) conduction system and of sinus node function] and extrinsic (vagal reflexes). Intrinsic and extrinsic mechanisms often coexist in the same patient, especially in the case of sick sinus syndrome.

To establish a strong correlation between syncope and bradycardia (especially when it is intermittent) is the major challenge for diagnostic evaluation and a prerequisite for pacing efficacy. Indeed, syncope is a transient symptom and not a disease. Typically, patients are asymptomatic at the time of evaluation and the opportunity to capture a spontaneous event during diagnostic testing is rare. Knowledge of what occurs during a spontaneous syncopal episode is ideally the gold standard for syncope evaluation. For this reason, it is likely that implantable monitors will become increasingly important in the assessment of the syncope patient, instead of, or before, many current conventional investigations. The issue is made more difficult by the fact that, when a cardioinhibitory vagal reflex is involved in causing syncope, this is almost always associated with a hyposympathetic vasodepressor reflex. The relative magnitude of the cardioinhibitory and vasodepressor reflexes varies from subject to subject and, to a lesser extent, from event to event. A dominant vasodepressor reflex is often responsible for the cases of failure of pacing therapy to prevent syncopal recurrences.

Atrioventricular block

Permanent AV block frequently causes symptoms owing to low cardiac output but only seldom causes syncope. Conversely, syncope is often the first clinical

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manifestation of a documented or undocumented intermittent AV block. In these latter cases, the cardiac rhythm may become dependent on subsidiary (often unreliable) pacemaker sites. Syncope occurs owing to the often long delay before these pacemakers begin to 'fire'. The correlation between syncope and bradycardia is usually easy when AV block is manifest [i.e. documented on electrocardiograph (ECG)]. In this case, cardiac pacing is likely to be effective. Bundle branch block is the most important predictor of undocumented AV block. Even if AV block is more likely in patients with an underlying structural heart disease, recent studies have shown that AV block is also present in a substantial number of patients without structural heart disease affected by unexplained syncope.[1–4] However, empirical pacing therapy without documentation of AV block carries a high risk of failure and should be limited to few situations in which there is a very high likelihood of block on clinical grounds. This is the case, for example, in a patient with bifascicular block and a history of syncope strongly suggestive of cardiac origin (recent onset recurrent syncope without prodrome and negative autonomic evaluation). In all the other cases in which AV block is suspected but not documented, careful cardiological investigations are recommended before embarking on cardiac pacing. Among these, electrophysiological study and prolonged ECG monitoring play the most important role.

Electrophysiological study has a low diagnostic sensitivity in the absence of bundle branch block, so its use is limited to patients with intraventricular conduction abnormalities. A prolonged baseline HV interval ($\geq$100 ms) or the development of intra or infra His two- or three-degree AV block at incremental atrial pacing or during pharmacological provocation with ajmaline, procainamide, or disopyramide during electrophysiological study has a high ($>$80%) predictive value and is considered sufficient to warrant a pacemaker implantation (class I indications of the Guidelines on Syncope of the European Society of Cardiology[5]). However, since $\sim$20% false-negative results can be expected, a negative electrophysiological investigation cannot rule out paroxysmal AV block as the cause of syncope, and further investigation, i.e. prolonged ECG monitoring, should be undertaken.[5]

Holter monitoring in syncope may be of more value if symptoms are very frequent. Daily single or multiple episodes of loss of consciousness might increase the potential for symptom–ECG correlation. In an overview[5] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients had correlation of symptoms with arrhythmia. The true yield of conventional ECG monitoring in syncope may be as low as 1–2% in an unselected population. Thus, Holter monitoring has limited diagnostic value in patients with syncope.

From the initial experience in patients with unexplained syncope, it appears that the implantable loop recorder might become the gold standard to be adopted when an arrhythmia is suspected to be the cause of syncope but not sufficiently proved to allow invasive treatment. AV block is one of the most frequent causes of syncope detected with implantable loop recorders both in patients with and without structural heart disease. Paroxysmal AV block was found in

- sixty-three per cent of the patients with bundle branch block who had a syncopal recurrence during the monitoring period[6];
- thirteen to sixteen per cent of the patients with narrow QRS with or without structural heart disease who had a syncopal recurrence during the monitoring period.[1,2,4]

Although formal randomized controlled trials have not been performed, it is clear from several old observational studies that pacing is able to improve survival in patients with heart block as well as to prevent syncopal recurrences (class I recommendation of the Guidelines on Syncope of the European Society of Cardiology[5]). Cardiac pacing virtually prevented syncopal recurrence in patients who had loop recorder documentation of paroxysmal AV block at the time of syncope.[3] No formal study has compared modes of pacing (VVI vs. DDD) in patients with paroxysmal AV block and syncope, and no alternative treatment exists.

Sick sinus syndrome

Definition, pathophysiology, and epidemiology

Sick sinus syndrome (SSS) is defined as a constellation of ECG abnormalities suggestive of sinus node dysfunction (persistent and inappropriate sinus bradycardia; sino-atrial block; sinus pauses; replacement of sinus rhythm by a junctional rhythm; long pauses after spontaneous or electrical cardioversion from atrial fibrillation) associated with symptoms such as syncope, pre-syncope, fatigue, etc.[7]

SSS is a multifaceted syndrome with different clinical presentations and prognoses in individual cases. Over a long period of time, SSS may slowly progress from sinus bradycardia to severe junctional rhythm or permanent atrial fibrillation. The mortality rate is similar in symptomatic (i.e. with syncopal spells) and asymptomatic patients and is not different to that of general population.[8] Indeed, survival is mainly affected by the presence of structural heart disease and complications such as systemic embolism or myocardial ischaemia.

Intrinsic SSS is due to an alteration of intrinsic sinus node properties, expression of a structural damage (fibrosis) of sinus node region, often a consequence of a diffuse process involving atrial and ventricular myocardium. On the contrary, extrinsic SSS is a disturbance of extrinsic regulation of sinus node activity secondary to a disorder of the autonomic nervous system, or to neurohumoral, hormonal, and pharmacological agents (antiarrhythmic drugs, beta-blockers, digoxin, verapamil, etc). In the clinical practice, however, the differentiation between the two forms is frequently difficult and both intrinsic and extrinsic abnormalities may coexist in the same patient. Most of the symptoms of SSS are caused by decreased cerebral perfusion, and more than half of

the patients with SSS complain of syncopal episodes. In the majority of cases, syncope in patients with extrinsic SSS is caused by a neurally mediated reflex, and bradycardia may be only one of the components of this reflex that often also induces peripheral vasodilatation and hypotension. Moreover, reflex mechanisms may additionally be involved in syncopal spells occurring in patients with intrinsic SSS. Indeed, in these patients, there is frequently an overlap between SSS, carotid sinus hypersensitivity, and positivity to head-up tilt testing.[9]

The prevalence of SSS significantly varies from nation to nation, dependent on multiple factors such as regional discrepancies in pathology, and criteria used for the diagnosis. Among Western countries, the annual incidence of SSS requiring pacemaker implantation varies from 40 to 187 per million inhabitants, and patients with SSS account for almost 50% of total implants in the USA. SSS is more frequently observed in older people, with a peak occurring in the seventh decade of life. Men and women appear to be equally affected.[8]

SSS is a primary electrophysiological disorder in approximately one-half of the cases, whereas in the remaining 50% of patients, it is secondary to various structural heart diseases. Supraventricular tachyarrhythmias are associated with SSS, the so-called brady–tachy syndrome, in 40–60% of the cases, and permanent atrial fibrillation develops in up to 16% of cases during follow-up. An AV and/or intraventricular conduction disturbance is frequently observed in SSS patients, the so-called panconduction tissue disease. However, advanced AV block after pacemaker implantation for SSS occurs only in a minority of cases during follow-up, with an annual incidence of 0.6–5%.[8]

Clinical presentation and diagnosis

From the clinical point of view, SSS may be classified as asymptomatic (sinus node dysfunction) and symptomatic forms (true sick sinus syndrome) when major (syncope and pre-syncope) or minor (dizziness, fatigue, cognitive defects, palpitations, dyspnoea) symptoms are present; uncomplicated and complicated forms when complications such as systemic embolism, heart failure, and angina occur.

From ECG point of view, SSS may be classified in mild forms (diurnal sinus bradycardia <50 and >40 b.p.m. and nocturnal sinus bradycardia >30 b.p.m.); severe forms (diurnal sinus bradycardia <40 b.p.m. and nocturnal sinus bradycardia <30 b.p.m.); resting and effort forms when chronotropic incompetence (inadequate increase of heart rate $<65\%$ of norms for age and sex during exercise stress test) is present; permanent and intermittent forms; isolated forms, brady–tachy syndrome (when associated with supraventricular tachyarrhythmias such as atrial fibrillation, atrial flutter, and atrial tachycardia) and panconduction tissue disease (when associated with atrio-ventricular and/or intraventricular conduction disturbances).

The diagnosis of SSS may be difficult because of the slow and erratic course of the disease. The ECG abnormalities suggestive of impaired sinus node function are usually detected on the standard ECG and prolonged ambulatory ECG monitoring such as 24 h Holter recording, and other external/implantable event or loop recorders. Although no well-defined limits exist between normal and abnormal sinus rates (especially in well-trained aerobic athletes), in older people, sinus rate <40 b.p.m. and sinus pauses >2–3 s should be considered abnormal.

In order to evaluate sinus node dysfunction better, especially the mild or intermittent forms of the disease, many investigative manoeuvres and diagnostic tests have been introduced in clinical practice: exercise stress testing (used to evaluate chronotropic incompetence); atrial pacing during electrophysiological study; pharmacological tests; methods for evaluating disturbances of autonomic nervous system, such as autonomic blockade (used to differentiate between intrinsic and extrinsic SSS), and head-up tilt testing. These diagnostic procedures have proved useful in assessing the pathophysiology and the severity of SSS, allowing an appropriate therapeutic approach to the disease. However, with respect to the electrophysiological parameters of the evaluation of sinus node function, all the aforementioned tests have a quite low sensitivity and negative predictive value.

Definite SSS is diagnosed only when a clear cause/effect relationship between ECG abnormalities and symptoms can be established by means of standard ECG or prolonged ambulatory ECG monitoring. On the contrary, possible SSS is diagnosed when such a relationship is not demonstrable, but severe signs of sinus node dysfunction are present. According to ESC guidelines on syncope,[5] SSS may be reasonably surmised to be the cause of syncope when during electrophysiological study the corrected sinus node recovery time is >1000 ms.

Therapy

Because survival is not affected by SSS *per se*, treatment is aimed to ameliorate symptoms and to improve quality of life. Moreover, many patients without or with only mild symptoms probably do not need any treatment. In extrinsic SSS, the elimination of offending drugs, such as many antiarrhythmic drugs and some antihypertensive agents, may prevent symptoms. However, when the elimination of the culprit drug is not feasible, pacing may be necessary. The pharmacological therapy for SSS includes the use of antiarrhythmic drugs for treatment of atrial tachyarrhythmias and the use of anticoagulant agents to prevent systemic embolism. Theophylline may be indicated in SSS patients with only minor symptoms, and/or episodes of overt heart failure.[10] On the contrary, when syncope is the presenting problem, pacemaker implantation is the first-choice treatment.

Cardiac pacing

Although only a few observational studies have compared the effects of electrical therapy with the natural history of untreated patients, cardiac pacing seems able to relieve symptoms related to bradycardia. Thus, permanent pacemaker implantation is a widely accepted

therapy in SSS patients with recurrent syncope. However, syncope may recur in up to 20% of cases, in spite of normal pacemaker function, probably on the basis of a concomitant neurally mediated reflex with vasodilatation and hypotension.[5]

According to ACC/AHA/NASPE Guidelines for implantation of pacemakers,[11] as well as ESC Guidelines on management of syncope,[5] permanent cardiac pacing is a class I indication in SSS patients when there is a documented association (established by means of standard ECG or prolonged ambulatory ECG monitoring) between syncope or other symptoms of SSS and bradyarrhythmias (definite SSS), and in the presence of chrontropic incompetence. Pacemaker implantation must also be considered (class II indication) when such a relationship is not demonstrable (possible SSS) but severe signs of sinus node dysfunction are present: evidence of sinus bradycardia < 40 b.p.m. or sinus pauses > 3 s while awake; corrected sinus node recovery time > 1000 ms during electrophysiological study.

Since almost all SSS patients have some degree of important chronotropic incompetence, a rate-responsive pacemaker is recommended.[12] Physiological pacing (atrial or dual-chamber pacemakers) has been definitely shown to be superior to ventricular pacing. Indeed, patients with SSS treated with physiological pacing demonstrate a significant lower incidence of atrial fibrillation, a lower risk of heart failure hospitalizations, and an improvement in quality of life with respect to patients receiving ventricular pacemakers at an acceptable cost.[13,14] On the contrary, the benefits of physiological pacing regarding stroke,[15] cardiovascular mortality, and total mortality are less well established. One of the possible explanations of these negative results is that the benefits of AV synchronicity provided by dual-chamber pacing are offset by the high percentage of ventricular pacing that occurs in DDDR mode. Indeed, a number of studies suggest detrimental effects of ventricular desynchronization produced by long-term right ventricular apical pacing. Finally, VVIR pacing systems are frequently associated with pacemaker syndrome and may precipitate reflex hypotension.

In the absence of a concomitant neurally mediated reflex with peripheral vasodilatation and hypotension, patients with SSS and syncope should be treated with AAIR pacemakers, otherwise dual-chamber pacemakers are indicated (preferably with the rate-drop response algorithm). The existence of associated AV and/or intraventricular conduction disturbances (bundle-branch block) strongly suggests dual-chamber pacing. In brady–tachy syndrome, dual-chamber pacemakers with automatic mode switching are recommended in order to avoid undesirable acceleration of ventricular pacing rate as a consequence of atrial tachyarrhythmias. In patients with dual-chamber pacemakers, especially in those with episodes of heart failure and/or depressed left ventricular function, in order to avoid right ventricular (apical) pacing with its associated haemodynamic disturbance, long AV delay or the more recent minimal ventricular pacing algorithms should be considered.[13,16] Finally, single-lead VDD pacemakers are contraindicated.

Reflex (neurally mediated) syncope

Reflex syncope is undoubtedly the most common of all causes of fainting. The strategy of therapy in this subgroup of patients with syncope has only recently been studied and although obvious progress has been made in the last few years it still remains unsatisfactory. Before assessing the role of pacing in reflex syncope, two statements should be addressed: (i) this subtype of syncope carries a benign prognosis in the vast majority of cases and treatment should be adjusted to its benign nature, particularly in young patients; (ii) pacing is not a first-line treatment and many other options are at our disposal, including no treatment at all. Reflex syncope (the main causes of which are reported in the ESC Task Force on Syncope[5]) covers a wide spectrum of entities linked by their common mechanism: vasodilatation and/or bradycardia. It is obvious that pacing could counteract only the detrimental effects of excessive bradycardia but has no role in preventing vasodilatation and hypotension. This explains why pacing has no or only partial effectiveness in most cases of reflex syncope. Physicians and patients should be aware of this limitation. Syncope diagnosed according to the definition proposed by the guidelines of the European Society of Cardiology[5] is the key symptom, and pacing should not be proposed in its absence. This excludes other symptoms such as dizziness, light-headedness, and vertigo, which are outside the scope of treatment by pacing. Although some patients with orthostatic hypotension or situational syncope have been treated by pacing, the series are too limited and the results too contradictory to justify special consideration here. This section is, therefore, restricted to the role of pacing in patients with carotid and vasovagal syndromes and adenosine sensitive syncope.

Carotid sinus syndrome

It has long been observed that pressure at the site where the common carotid artery bifurcates produces a reflex that leads to slowing in heart rate and fall in blood pressure. In some individuals, an abnormal response to carotid massage (CSM) is observed. A ventricular pause lasting >3 s and/or a fall in systolic blood pressure of >50 mmHg defines carotid sinus hypersensitivity.[17] When associated with spontaneous syncope, an abnormal CSM defines the carotid sinus syndrome (CSS). Precise methodology and results of CSM are reported in the guidelines on syncope.[5] It should be emphasized that reproduction of symptoms during CSM is likely to increase the specificity of the test in respect to the finding of an asymptomatic carotid sinus hypersensitivity. Carotid sinus massage producing >3 s pause without symptoms has, in the past, not been considered to be a diagnosis warranting treatment, but recent work suggests that in syncopal patients with a positive CSM but without symptoms, pacing can now be entertained with likely benefit.[18]

Pacing was considered a therapeutic option for CSS in the early 1970s when some case reports demonstrated that recurrence of syncope was abolished after

implantation of a pacemaker.[19] Series then confirmed that pacing in patients with CSS could significantly reduce the numbers of syncopes.[20] Non-randomized comparative studies were in accordance with these preliminary results, and in the mid-1980s, pacing became a recognized treatment of CSS. The first randomised trial which compared pacing versus no pacing in 60 patients was reported in 1992.[21] After a mean follow-up of 36 $\pm$ 10 months, syncope recurred, respectively, in 9 and 57% of the patients in pacing and control groups ($P <$ 0.0002). In another study, patients with a cardioinhibitory response to CSM were implanted with a pacemaker designed to record asystolic episodes. Long pauses ($\geq$6 s) were detected in 53% of the patients during a 2-year follow-up period, suggesting that a positive response to CSM predicts the occurrence of spontaneous long ventricular pauses.[22]

As medical therapy for CSS was largely abandoned, cardiac pacing appeared as the only effective treatment for patients with CSS in the late 1990s. Although it has been argued that single-chamber ventricular pacing may be adequate, dual-chamber cardiac pacing is preferred.[23] Some dual-chamber pacemakers with sophisticated algorithms were designed to limit hypotension. These algorithms, based on acceleration of the pacing rate when intrinsic heart rate suddenly decreases, gave favourable results during acute testing[24] but well-designed trials demonstrating their effectiveness during long-term follow-up are missing.

Vasovagal syncope

Vasovagal syncope (VVS) represents $\sim$50% of all causes of fainting.[25] In the vast majority of cases, the diagnosis can be made solely by a typical history. However, in some cases, tilt testing remains the key procedure to identify the vasovagal origin of syncope. Data from controlled trials showed that, in 50% of patients, tilt testing became negative whether the test was repeated with treatment or placebo.[26] Furthermore, acute studies were not predictive of the long-term outcome of pacing therapy.[27] Finally, the mechanism of tilt-induced syncope was frequently different from what was observed during spontaneous syncope recorded with implantable loop recorder.[28] These data suggest that tilt testing has no or limited value for assessing the effectiveness of treatments, particularly pacing.

Non-pacing therapy in vasovagal syncope

Present treatments of VVS are based on an incomplete understanding of the pathophysiology. Patients who seek medical advice after having experienced VVS require firstly reassurance and education regarding the benign nature of the disease. Recently, efficacy of physical counter manoeuvres has been reported in well-designed trial.[29]

Pacing in vasovagal syncope: non-randomized trials

Rationale for pacing in patients with VVS was based on the observation of spontaneous or tilt-induced long ventricular pauses. Since that time pacing has been the subject of some observational studies[30] demonstrating its effectiveness in highly selected patients.

Pacing in vasovagal syncope: randomized trials

Effectiveness of pacing has been studied in five multicentre randomized controlled trials,[31–35] three non-blinded[31–33] gave positive results and two blinded[34,35] gave negative results. The strongest supporting evidence was provided by the North American VPS[32] and the European VASIS and SYDIT trials.[31,33] After publication of these trials, pacing was accepted as a treatment for patients with frequent VVS. The Second Vasovagal Pacemaker Study (VPS II)[34] and the Vasovagal Syncope and Pacing trial (SYNPACE)[35] gave totally different results. They diverged from the previous trials in that patients in the control arm received a permanent pacemaker programmed 'off'. Although there was a 30% reduction in recurrence in the two groups, the VPS II study failed to demonstrate significant superiority of pacing. In the SYNPACE trial, syncope recurred in 50% of patient assigned to pacing 'on' and in 38% of patients assigned to pacing 'off'. All these studies have limitations and further studies without these limitations (particularly the pre-implant selection criteria) need to be completed before pacing can definitely be considered ineffective. However, the ineffectiveness of pacing would not be surprising if it is considered that it could be only effective in avoiding ventricular pauses but has no role in preventing vasodilatation and hypotension, frequently the dominant mechanism leading to VVS. A study using implantable loop recorders[36] concluded that only half of the patients had an asystolic pause recorded at the time of spontaneous VVS. The role of the implantable loop recorder to select patients who might benefit from pacing has recently been proposed.[1] In the ISSUE II trial,[1] patients $>$40 years with a high likelihood of VVS received an implantable loop recorder and those who experienced syncope with concomitant long pauses received a pacemaker. The results were clearly in favour of pacing but unfortunately ISSUE II was not a randomized trial and a final conclusion cannot be drawn. Anyway, it must be underlined that the decision to implant a pacemaker needs to be kept in the clinical context of a benign condition which frequently affects young patients in whom tolerance of pacemakers and leads for several decades is likely to be associated with complications. Thus, cardiac pacing presently may have a role in a selected proportion of old patients affected by severe recurrent unpredictable VVS.

Adenosine-sensitive syncope

In spite of extensive evaluation, 20–30% of patients with syncope are discharged without precise diagnosis. This observation led to evaluation of new tests to investigate patients with syncope of unknown origin. Among these tests, injection of a bolus of 20 mg of adenosine was considered useful and gained acceptance.[36] Methodology and positive criteria of the test were precisely reported in previous papers.[36] In a substantial number of patients without a diagnosis of the cause of syncope (probably

between 5 and 10%), the only finding was an abnormally long ventricular pause during injection of adenosine. This long pause was due to the sudden onset of AV block; sinus rhythm returned usually within a few seconds. This seemed to justify treatment of these patients with pacing. This therapy was tested in only one randomized series of 20 patients.[37] The results were in favour of pacing: after a mean follow-up of 52 months ($P < 0.02$), but they were challenged by those of several observational series of patients with a positive ATP test. In some of these patients, syncopal recurrences were registered by an implantable loop recorder: only 50% of them had bradycardia.[38,39] Finally, there is no well-designed study able to answer the question of the value of pacing in adenosine-sensitive syncope.

Conclusions and perspective

Syncope should be considered as the historical and key symptom that has justified emergence of pacing in the therapeutic armamentarium. In this setting, indications are presently stable, and except some limited modifications, for example, in reflex syncope, it is improbable that very innovative indications will emerge. Finally, development could come from new technologies limiting the adverse events associated with leads and pacemaker implantation: dramatic reduction in the size of the hardware allowing less invasive or no surgery, direct implantation of the generator into the heart excluding the need for a lead. All these ideas appear as unrealistic now as was the idea of pacing the heart to prevent syncope complicating severe bradycardia 50 years ago.

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